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***Title:*** **Changes in the requirement for early surgery in inflammatory bowel disease in the era of biological agents.**

***Short Title:*** Anti-TNF availability and surgery of IBD.

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**Background & Aims:** Biological therapies may be changing the natural history of inflammatory bowel diseases, reducing the need for surgical intervention. We aimed to assess whether the availability of anti-TNF agents impacts the need for early surgery in Crohn's disease (CD) and ulcerative colitis (UC). **Methods:** Retrospective, cohort study of patients diagnosed within a 6-year period before and after the licensing of anti-TNFs (1990-1995 and 2007-2012 for CD; 1995-2000 and 2007-2012 for UC) were identified in the ENEIDA Registry. Surgery-free survival curves were compared between cohorts. **Results:** A total of 7,370 CD patients (2,022 in Cohort 1 and 5,348 in Cohort 2) and 8,069 UC patients (2,938 in Cohort 1 and 5,131 in Cohort 2) were included. Immunosuppressants were used significantly earlier and more frequently in both CD and UC post-biological cohorts. The cumulative probability of surgery was lower in CD following anti-TNF approval (16% and 11%, 22% and 16%, and 29% and 19%, at 1, 3 and 5 years, respectively $p<0.0001$), though not in UC (3% and 2%, 4% and 4%, and 6% and 5% at 1, 3 and 5 years, respectively; $p=0.2$). Ileal involvement, older age at diagnosis and active smoking in CD, and extensive disease in UC, were independent risk factors for surgery, whereas high-volume IBD centres (in both CD and UC) and immunosuppressant use (in CD) were protective factors. **Conclusions:** Anti-TNF availability was associated with a reduction in early surgery for CD (driven mainly by earlier and more widespread immunosuppressant use) but not in UC.

***Keywords***: inflammatory bowel disease; surgery; anti-TNF; immunosuppressants.

## INTRODUCTION

Although inflammatory bowel disease (IBD) is generally managed medically, surgery is still indicated in a proportion of patients due to refractoriness to medical therapy (particularly in ulcerative colitis -UC-) or disease-related complications (particularly in Crohn's disease -CD-). The risk of post-operative complications in these patients is high[1]. Moreover, in CD, surgery is not curative, disease recurrence is extremely common, and large or repeated resections may lead to the loss of intestinal function[2]. In UC, although proctocolectomy is considered to be curative, ileostomies are not free from complications and, if an ileo-anal pouch is created, there is an important risk of pouchitis[3].

The irruption of biological agents in the late nineties sparked a revolution in the management of IBD and raised great expectations of a better control of the disease. Given that the assessment of the impact of anti-TNF agents on the natural history of IBD requires a long-term follow-up and that most RCTs are designed to generate short-term results, surrogate markers of good prognosis, such as mucosal healing, were progressively included as secondary endpoints in clinical trials. In fact, a number of controlled studies showed that anti-TNF therapy was associated with a reduced rate of intestinal resections and colectomies, but in highly selected patients and only compared to placebo-treated groups[4,5]. However, large-scale studies assessing the impact of the availability of biological agents on the natural history of IBD in real life are still lacking. Moreover, the way we use anti-TNF agents has evolved from the early days when infliximab was licensed for CD: on-demand therapy has given way to scheduled maintenance therapy, initial combination therapy with immunosuppressants has been widely adopted to reduce immunogenicity and increase treatment efficacy and persistence, and anti-TNF therapy has been introduced progressively earlier in the disease course. In contrast, when the first anti-TNF agent was approved for UC, the use of these drugs was already standardized in IBD.

The aim of the present study was to assess, in large cohorts and in clinical practice, the need for early surgery (within the first 5 years from disease diagnosis) before and after the availability of anti-TNF agents, in both CD and UC.

## MATERIALS AND METHODS

The study included two incident cohorts accounting for the 6-year periods immediately before and after the approval of the first anti-TNF agent for CD, as well as for UC. Since approval for the first anti-TNF agent for CD (infliximab) was granted in 1999, incident CD cases registered in the prospectively-maintained ENEIDA registry[6] diagnosed from 1990 to 1995 and from 2007 to 2012 were identified. We chose not to use the period 2000-2005 for the second CD cohort because infliximab was the first biological agent ever approved for the treatment of IBD and its use changed within the first years after approval, not only in terms of the number of patients treated but also in the treatment schedule, going from single "on demand" administrations to well-established induction and maintenance regimens. Similarly, since the approval of the first anti-TNF agent (infliximab) for UC was in 2005, the incident UC cases in the registry diagnosed from 1995 to 2000 and from 2007 to 2012 were identified. In line with the purpose of this study, patients were followed-up for the first 5 years from disease diagnosis, or until surgery (colectomy for UC, intestinal or colon resections for CD), loss of follow-up or death if any occurred within the first 5 years from diagnosis. Those patients lacking a date of diagnosis, date of surgery, or type of surgery, those in whom the date of surgery preceded by more than 1 month the date of diagnosis, those with a change in the initial diagnosis (from CD or IBD unclassified to UC, or vice versa), and those with a follow-up period after diagnosis shorter than 6 months (in the absence of surgery), were not included.

The primary outcome was *early surgery*, as defined by the need to perform intestinal resection, segmental or subtotal colectomy, or proctocolectomy (excluding perianal surgeries and drainage of abdominal abscesses) within the first 5 years from disease diagnosis. Regarding the use of immunosuppressants (IMS) and anti-TNF agents, we only considered those patients on whom IMS or anti-TNFs were used within the first 5 years and before surgery if surgery occurred.

### Statistical analysis

Results are expressed as frequencies and percentages, mean ± SD or median and interquartile range (IQR). Statistical differences between groups were assessed using the $\chi^2$ test, the Fisher exact test, and the Student t test, as needed. Kaplan-Meier curves were constructed to assess the impact of anti-TNF availability on the need early surgery. The log-rank test was used to detect

overall statistical differences between survival curves. To adjust the effect of the availability of anti-TNF agents on surgery-free survival to the effects of other potential confounding factors including ileal CD involvement, extensive UC, active smoking at diagnosis, high-volume IBD centres (as defined by including more than the median number of patients per centre in this study), or exposure to IMS, a Cox regression multivariate analysis was performed separately for both the UC and CD cohorts in their entirety. In all instances, statistical significance was set at $p<0.05$.

## RESULTS

A total of 7,370 CD patients were included, 2,022 in Cohort 1 (before anti-TNF availability) and 5,348 in Cohort 2 (after the first anti-TNF was approved) (**Table 1** ). Of note, patients in Cohort 1 were significantly younger and included a significantly higher proportion of active smokers at diagnosis. The date of the occurrence of extraintestinal manifestations is not collected in the Eneida registry, and, due to a longer follow-up beyond the 5-year study period in the registry, a significantly higher incidence of extraintestinal manifestations was therefore also observed in Cohort 1.

Regarding UC, 8,069 patients were included, 2,938 in Cohort 1 and 5,131 in Cohort 2 (**Table 2**). Cohort 1 had a higher proportion of extensive UC and contained a significantly higher proportion of active smokers and a younger age at diagnosis. As with the CD cohorts, since these patients had a longer follow-up in the registry beyond the study period, UC-related complications (toxic megacolon, concomitant sclerosing cholangitis, and extraintestinal manifestations) were significantly more frequent in Cohort 1.

### Use of immunosuppressants and anti-TNF agents

Three-hundred and twenty-five (17%) and 3,402 (64%) CD patients were exposed to IMS within the first 5 years in Cohorts 1 and 2, respectively ($p<0.0001$). IMS were prescribed both more often and earlier among patients in Cohort 2 (27.3±18.2 *vs.* 10.3±13.2 months, $p<0.0001$). Therefore, the cumulative probabilities of being exposed to IMS in Cohorts 1 and 2 were 5% and 51% at 1 year, 11% and 62% at 3 years, and 18% and 74% at 5 years, respectively ($p<0.0001$) (**Figure 1**). Finally, 1,952 patients in Cohort 2 (36%) were exposed to anti-TNF agents within 5 years from disease diagnosis, after a mean time of 17.2±15.7 months. The cumulative probability of being exposed to anti-TNF agents in Cohort 2 was 21%, 37% and 45%, at 1, 3 and 5 years, respectively.

Regarding UC, 472 (16%) and 1,479 (29%) patients were exposed to IMS within the first 5 years in Cohorts 1 and 2, respectively ($p<0.0001$). As in CD, IMS were not only prescribed more often but also earlier among patients in Cohort 2 (23.3±17.6 *vs.* 16.2±16.3 months, $p<0.0001$). Therefore, the cumulative probabilities of being exposed to IMS in Cohorts 1 and 2 were 6%

and 17% at 1 year, 12% and 27% at 3 years, and 18% and 34% at 5 years, respectively (p<0.0001) (**Figure 1**). Finally, 762 UC patients in cohort 2 (15%) were exposed to anti-TNF agents within 5 years from disease diagnosis, after a mean time of 22.4±17 months. The cumulative probability of being exposed to anti-TNF agents in Cohort 2 was 6%, 13% and 18%, at 1, 3 and 5 years, respectively.

**Early surgery**

A total of 1,506 (20%) patients in CD cohorts underwent surgery within the study period, after a median time of 8.4 months from diagnosis (IQR,0-26). Most of the patients underwent ileal or ileocolic resections (94%), and the main indication was intestinal stenosis (37%), followed by disease refractoriness and disease-related penetrating complications (19% each). In Cohort 1, 573 (28%) patients were operated on within the first 5 years, compared to 933 (17%) patients in Cohort 2 (p<0.0001). Again, surgeries were both more common and performed earlier in Cohort 1, with a median time for early surgery of 9.9 months (IQR,0-31.6) in Cohort 1 *vs.* 14.6 months (IQR,0.4-24.1) in Cohort 2 (p=0.029). Of note, in Cohort 1, only 61 of these 573 operated patients (11%) were exposed to IMS before surgery, resulting in a significantly lower rate of exposure to IMS before surgery than in Cohort 2 in which 432 of 933 (46%) were exposed (p<0.0001). Conversely, the proportion of patients exposed to IMS who were finally operated on at the end of the study period was 33% in Cohort 1 and 21% in Cohort 2 (p<0.0001). Two hundred and ninety-seven (32%) of the 933 operated patients in Cohort 2 were exposed to anti-TNF agents prior to surgery, and only 15% of the patients exposed to anti-TNFs were finally operated on.

The cumulative probabilities of intestinal resection in Cohorts 1 and 2 were 16% and 11% at 1 year, 22% and 16% at 3 years, and 29% and 19% at 5 years, respectively (p<0.001) (**Figure 2**). In the univariate analysis, ileal involvement, active smoking, older age no use of IMS, and low-volume IBD centres were significantly associated with surgical requirements. In the Cox regression analysis, ileal involvement, active smoking at diagnosis, and older age at diagnosis increased the risk of early surgery, whereas the use of IMS and high-volume IBD centres reduced it. We observed a marked but statistically non-significant trend towards the influence of anti-TNF availability as reflected in the study cohort (**Table 3**).

A total of 367 (5%) patients in the UC cohorts underwent surgery within the study period, after a median time of 14.5 months from diagnosis (IQR,1.5-33.6). In Cohort 1, 156 (5%) patients were operated on within the first 5 years compared to 211 (4%) patients in Cohort 2 (p=0.013). Contrarily to what occurred in CD, the mean time for early surgery was similar in both cohorts (18.3±18.3 months in Cohort 1, and 20±18.2 months in Cohort 2; p=0.3). Of note, in Cohort 1, only 50 out the 156 operated patients (32%) were exposed to IMS before surgery and this resulted in a significantly lower proportion than in Cohort 2, in which 118 out of 211 (56%) were exposed to IMS (p<0.0001). The proportion of patients exposed to IMS who had undergone surgery at the end of the study period was significantly higher in Cohort 1 than in Cohort 2 (11% *vs.* 8%, respectively; p<0.023). In Cohort 2, 23 of the 211 operated patients (58%) were exposed to anti-TNF agents prior to surgery, and 16% of them were finally operated on.

The cumulative probabilities of colectomy in Cohorts 1 and 2 were 3% and 2% at 1 year, 4% and 4% at 3 years, and 6% and 5% at 5 years, respectively (p=0.2) (**Figure 3**). In the univariate analysis, extensive colitis, male gender, older age, no use of IMS, and low-volume IBD centres were significantly associated with colectomy requirements. In the Cox regression analysis, only extensive UC increased the risk of early colectomy, whereas high-volume IBD centres reduced it; we did not observe any influence of being in Cohort 1 or 2 (**Table 3**).

## DISCUSSION

In recent years, many population-based studies and meta-analyses observed a marked reduction in surgery rates for CD and a less pronounced reduction for UC[7-9]. The high clinical efficacy of anti-TNF agents raised the idea that they might change the natural history of IBD; however, those studies assessing the impact of the early introduction of IMS and anti-TNFs in CD on surgery rates have reported conflicting results[10-12]. Moreover, a recent retrospective study on the management of IBD based on the database of the French national health insurance system from 2009 to 2013, observed that the step-up approach continues to be the predominant therapeutic strategy[13].

We specifically designed this study to focus on the impact of the availability of anti-TNF agents on the need for surgery within the first 5 years of disease. Although this might be seen as a drawback of our study, most surgeries are performed shortly after diagnosis in both CD and UC[7,8]. In CD, a substantial proportion of patients present with fistulizing or stricturing complications, leading to a surgical approach. Moreover, if IMS or anti-TNF had the potential to modify the natural history of the disease, this should occur early in the course of the disease, as suggested in a recent paediatric study[12]. In UC, population-based studies have shown that colectomies due to medical refractoriness are performed mainly within the first two years from diagnosis. Finally, we also performed subanalyses in those populations at a higher risk for surgery: with ileal involvement in CD[14] and extensive UC[15,16].

In CD, our exposure rates to IMS and anti-TNF were very similar to those reported in a French, population-based study including almost 35,000 incident CD patients from the period 2009-2013[13]. Our observed cumulative probabilities of surgery in CD were also in line with those of the most recently published population-based studies. A retrospective study using a primary care database from the United Kingdom including 3,059 incident CD patients from the period 1994-2014, observed a cumulative probability of first surgery at 1 and 5 years of 9% and 18% during the period 1996-2001, and 13% and 22% during the period 2008-2013, respectively[9]. In the abovementioned French study, the cumulative probabilities of surgery at 1 and 5 years were 6% and 13%, respectively[13]. Finally, in another cohort of incident CD from the period 2003-2011, even with a lower exposure to IMS and anti-TNFs, cumulative probabilities at 1 and 5 years were 9% and 23%, respectively[8]. Although our study was designed to assess the impact of anti-TNF

availability on early surgery, the differences between the two CD cohorts might not be related only to the use of anti-TNFs. Although surgery was more frequent at the time of CD diagnosis in cohort 1 (probably due to a greater diagnostic delay at that time), the use of IMS in CD was associated with a significant reduction in the need for surgery, in addition to ileal involvement and active smoking, the most repeatedly reported risk factors for surgery in CD. In agreement with our observation, some smaller but well-designed studies observed a significant correlation between the early use of thiopurines and a reduction in surgical rates[10,14,17]. The implementation of IBD multidisciplinary units may also have an impact on this, although its assessment was not feasible in the present study. Unexpectedly, we also found that older age at diagnosis was associated with an increased risk of early surgery; A possible explanation for this is that differential diagnosis may be difficult in elderly patients (particularly with ischemic ileitis or colitis) prompting surgical resection instead of starting steroids or IMS empirically.

In UC, despite a more frequent and earlier use of IMS in Cohort 2, we did not observe any impact of anti-TNF availability on surgery rates. Our figures are in agreement with those reported in population-based studies in which only incident cases from 2000 onwards were included[7,13]. Although a decrease in surgery rates in UC has been reported in recent decades, there are only a few published studies in UC focusing on this issue, most of which have a small sample size and included incident cohorts from the 1970s and 1980s[7]. It has been suggested that the implementation of the Oxford criteria for predicting steroid-refractoriness in clinical practice (which preceded infliximab availability by almost a decade) and the widespread use of cyclosporine as a rescue therapy in this scenario may have played a role in this progressive reduction in the need for surgery[18], precluding a clear impact of infliximab availability on UC. In addition, the difference in the proportion of UC patients who were exposed to IMS in Cohorts 1 and 2 who were finally operated on was slightly lower than that observed in CD, suggesting that the effect of IMS in UC may be not the same as in CD. In fact, extensive UC was the only factor associated with a higher risk for colectomy in the Cox regression analysis.

The main strengths of our study are its chronologic design and sample size, though it also has some limitations. We excluded patients with unclassified IBD and those whose initial IBD type was changed. Although this accounted for a small number of patients, we considered that the clinical management (and, particularly, the decision to adopt a surgical approach) might have

been markedly different and could bias the results. Secondly, the Eneida registry was initially started in 2006 and the number of participating centres increased exponentially from then on. Although the registry is prospectively maintained, when a centre starts its participation in the registry the existing patients can be included retrospectively and, in every participating centre, those patients who were lost to follow-up before the implementation of the registry may have not been included. Of course, this is a drawback of our study, and explains the higher number of incident cases in the latter cohorts, although it is minimized by the fact that surgery, immunosuppressant and biological therapies are mandatory variables in the registry and are rarely missed. Moreover, we only took into account the exposure to anti-TNF agents but not its type, need for dose-escalation or the concomitant use of IMS. Of course, the way anti-TNF are used (in combination therapy, driven by drug trough levels, or detailed policies for dose-escalation) might have an impact on surgical requirements.

In summary, in a large study assessing surgery requirements in incident CD and UC cohorts in the immediate pre and post-biological agents licensing periods, we observed that IMS are used earlier and more frequently in the biological era, and that this was associated with a reduction in surgery rates in CD, though not in UC.

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***APPENDIX**. **Complete affiliations of the investigators of the GETECCU Eneida Registry**.

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**Table 1.** Baseline characteristics of patients with Crohn's disease.

| | *Cohort 1* *1990-1995* (n=2,022) | *Cohort 2* *2007-2012* (n=5,348) | P-value |
|---|---|---|---|
| Female gender | 1,026 (51) | 2,587 (48) | 0.07 |
| Age at diagnosis | 28.8 ± 11.7 | 36.9 ± 16.2 | <0.0001 |
| Active smoking at diagnosis | 872 (44) | 1,993 (37) | <0.0001 |
| Familial IBD | 294 (15) | 704 (13) | 0.1 |
| Upper gastrointestinal tract involvement | 351 (17) | 917 (17) | 0.8 |
| Ileal involvement | 1,632 (81) | 4,303 (80) | 0.8 |
| Colon involvement | 1139 (56) | 2581 (48) | <0.0001 |
| Intestinal stenosis | 238 (12) | 586 (11) | 0.32 |
| Intraabdominal penetrating complications | 167 (8) | 396 (7) | 0.22 |
| Perianal disease | 178 (9) | 435 (8) | 0.35 |
| Extraintestinal manifestations[†] | 608 (31) | 1,003 (19) | <0.0001 |

[†]data extracted at the last encounter (not at the end of the study follow-up period).

**Table 2.** Baseline characteristics of patients with ulcerative colitis.

| | *Cohort 1* *1990-1995* (n=2,938) | *Cohort 2* *2007-2012* (n=5,131) | P-value |
|---|---|---|---|
| Female gender | 1,323 (45) | 2,415 (47) | 0.07 |
| Age at diagnosis | 37 ± 14.1 | 41.7 ± 16.4 | <0.0001 |
| Active smoking at diagnosis | 536 (18) | 677 (13) | <0.0001 |
| Familial IBD | 318 (11) | 539 (11) | 0.5 |
| Extensive colitis† | 1,237 (42) | 1,903 (37) | <0.0001 |
| Extraintestinal manifestations† | 511 (17) | 589 (11) | <0.0001 |
| Sclerosing cholangitis† | 44 (2) | 41 (1) | 0.009 |
| Toxic megacolon† | 50 (2) | 40 (1) | <0.0001 |

†data extracted at the last encounter (not at the end of the study follow-up period).

**Table 3**. Factors associated with early surgery (multivariate Cox regression analysis).

| | *HR [IC 95%]* | *P-value* |
|---|---|---|
| **Crohn's Disease** | | |
| Ileal involvement | 2.83 [2.01-2.83] | <0.001 |
| Older age at diagnosis | 1.01 [1.004-1.01] | <0.001 |
| Active smoking at diagnosis | 1.20 [1.08-1.33] | 0.001 |
| Use of immunosuppressants | 0.46 [0.42-0.52] | <0.001 |
| High-volume IBD centres | 0.73 [0.63-0.85] | <0.001 |
| Cohorts 1 *vs.* 2 | 0.88 [0.78-1.003] | <0.056 |
| **Ulcerative Colitis** | | |
| Extensive colitis | 3.33 [2.68-4.15] | <0.001 |
| Older age at diagnosis | 1.003 [0.99-1.01] | 0.39 |
| Active smoking at diagnosis | 0.81 [0.60-1.09] | 0.17 |
| High-volume IBD centres | 0.63 [0.48-0.84] | 0.002 |
| Cohorts 1 *vs.* 2 | 0.90 [0.73-1.11] | 0.31 |

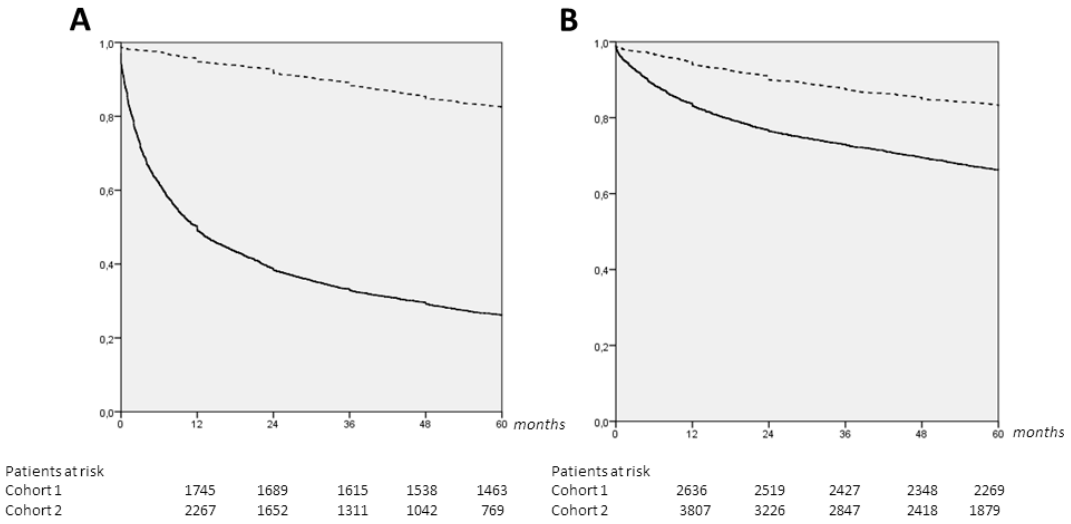


**Figure 1.** Cumulative probability of remaining free of immunosuppressants in (A) Crohn's disease and (B) Ulcerative Colitis (Cohorts 1, dotted line; Cohorts 2, black line).

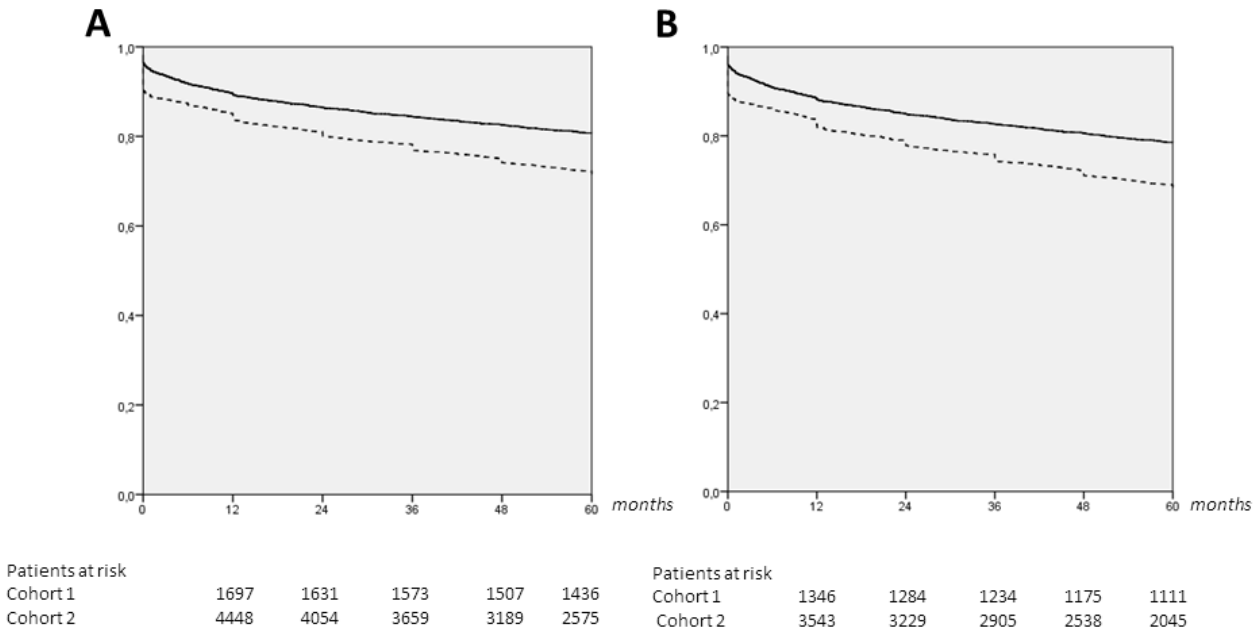


**Figure 2.** Cumulative probability of remaining free of intestinal resection in Crohn's disease. (A) whole cohort; (B) only in patients with ileal involvement (Cohorts 1, dotted line; Cohorts 2, black line).

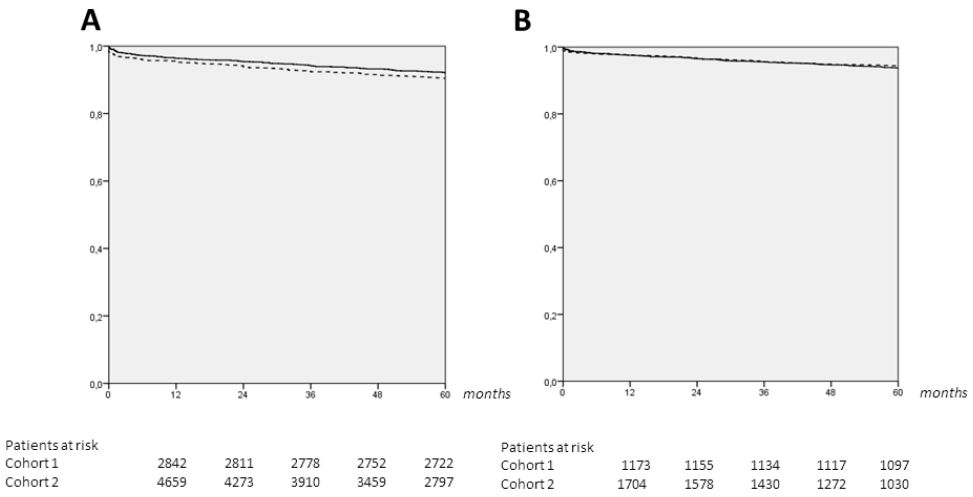


**Figure 3.** Cumulative probability of remaining free of colectomy in ulcerative colitis. (A) whole cohort; (B) only in patients with extensive disease (Cohorts 1, dotted line; Cohorts 2, black line).